Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Efmody 5mg modified-release hard capsules
Efmody 10mg modified-release hard capsules
Efmody 20mg modified-release hard capsules

hydrocortisone

PLGB 50616/0011
PLGB 50616/0012
PLGB 50616/0013

Diurnal Europe B.V.

LAY SUMMARY

Efmody 5, 10 & 20mg modified-release hard capsules (hydrocortisone)

This is a summary of the Public Assessment Report (PAR) for Efmody 5, 10 & 20mg modified-release hard capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Efmody in this lay summary for ease of reading.

For practical information about using Efmody, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Efmody and what is it used for?
These are applications for hybrid medicines. This means that the medicine is similar to reference medicines already authorised in the European Union called Hydrocortisone 10 and 20 mg tablets, albeit with certain differences. In this case, Efmody is available in a different pharmaceutical form (modified release tablets), a different strength and has a specific clinical use.

Efmody is used when the adrenal gland is not making enough cortisol due to an inherited condition called congenital adrenal hyperplasia. It is for use in adults and adolescents from 12 years of age.

How does Efmody work?
Efmody contains the active substance hydrocortisone. Hydrocortisone belongs to a group of medicines known as corticosteroids. Hydrocortisone is a copy of the hormone cortisol.

How is Efmody used?
The pharmaceutical form of these medicines is a modified-release hard capsule and the route of administration is oral.

A doctor will decide on the right starting dose of Efmody and then adjust the dose, as needed. During illnesses, around the time of surgery and during times of serious stress, a doctor may request that a patient take another corticosteroid medicine instead of, or as well as, Efmody.

The initial daily dose may be divided into two doses, with two-thirds to three-quarters of your daily dose in the evening at bedtime and the rest given in the morning.

The morning dose of hydrocortisone modified-release hard capsules should be taken on an empty stomach at least 1 hour before a meal and the evening dose taken at bedtime at least 2 hours after the last meal of the day.

For further information on how Efmody is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor has told them. The patient should check with their doctor if they are not sure.

What benefits of Efmody have been shown in studies?
The benefits of Efmody have been shown in a main study involving 122 patients with congenital adrenal hyperplasia. Efmody was compared with standard treatment involving other corticosteroid medicines. The main measure of effectiveness was a score based on levels of 17-hydroxyprogesterone (17-OHP), a hormonal substance that indicates increased male sex hormones in uncontrolled congenital adrenal hyperplasia. A fall in this score over the course of the study showed better control. Over the 24 weeks of the study this score fell by 0.403 in patients treated with Efmody, compared with 0.172 in those given standard treatment. Although this difference was not sufficient to clearly show that Efmody worked better than standard treatment, measurements also suggested a better control of morning 17-OHP levels.

Supportive data from an ongoing continuation study indicated that control of congenital adrenal hyperplasia could be maintained with Efmody longer term.

What are the possible side effects of Efmody?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Efmody approved?
Efmody provides adequate control of congenital adrenal hyperplasia and the overall data suggests an improved hormone balance. The long-term data suggests this could be maintained, in some cases using lower doses of corticosteroid than before and thus reducing the risk of side effects from long-term treatment.

Modified-release hydrocortisone is considered to offer clinical value by allowing dosing that resembles the daily rhythm of natural cortisol secretion. The reported side effects of Efmody are in line with those expected for hydrocortisone taken by mouth.

What measures are being taken to ensure the safe and effective use of Efmody?
A Risk Management Plan (RMP) has been developed to ensure that Efmody is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Efmody
These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales) following a European Commission (EC) decision on 27 May 2021 (EMEA/H/C/005105), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

Marketing authorisations were granted in Great Britain to Diurnal Europe B.V. on 01 July 2021 (PLGB 50616/0011-13).

The full PAR for Efmody follows this summary.

This summary was last updated in August 2021.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Efmody 5, 10 & 20mg modified-release hard capsules (PLGB 50616/0011-13) could be approved.

The products are approved for the following indications:
Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.

The name of the active substance is hydrocortisone. Hydrocortisone is a glucocorticoid. Glucocorticoids have multiple effects in multiple tissues through actions on the intracellular steroid receptors.

Please note that these were initially assessed by MHRA as centralised applications. From 01 January 2021, these applications were assessed by MHRA as national applications. These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales) following a European Commission (EC) decision on 27 May 2021 (EMEA/H/C/005105), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 52 of the Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended).

These applications were evaluated for fulfilment of orphan designation criteria and were examined by the Commission on Human Medicines (CHM) on 27/28 May 2021. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was not satisfactorily demonstrated. Please see Annex 1 for a summary of the orphan refusal.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted in Great Britain to Diurnal Europe B.V. on 01 July 2021 (PLGB 50616/0011-13).

II. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL
The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS
MHRA considered that the quality data submitted for these applications are satisfactory.

The grant of marketing authorisations is recommended.

IV. NON-CLINICAL ASPECTS
MHRA considered that the non-clinical data submitted for these applications are satisfactory.

The grant of marketing authorisations is recommended.

V. CLINICAL ASPECTS
MHRA considered that the clinical data submitted for these applications are satisfactory.

The grant of marketing authorisations is recommended.

VI. RISK MANAGEMENT PLAN (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VII. USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

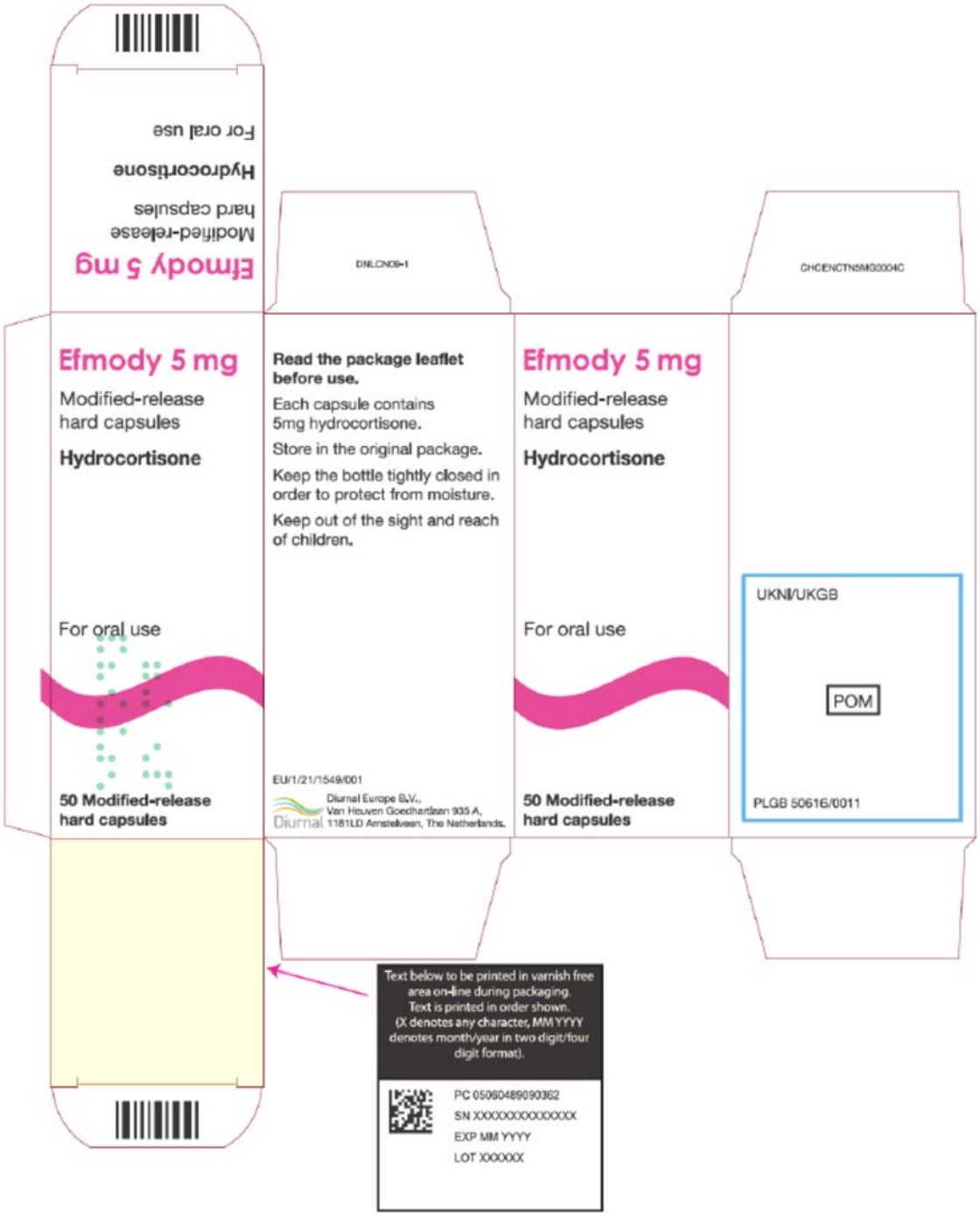
The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

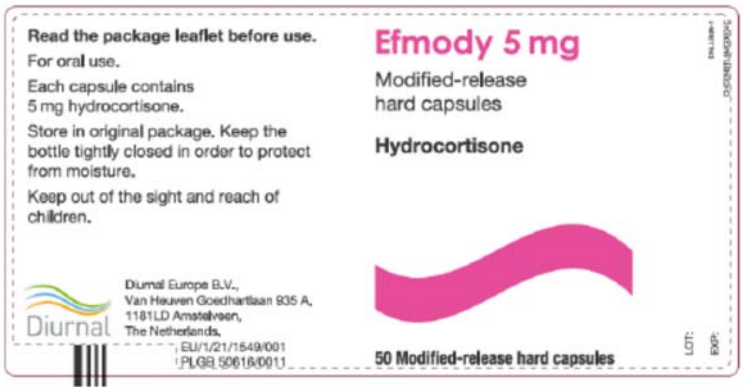
VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.


Efmody 5 mg
Modified-release
hard capsules
Hydrocortisone
For oral use
DNLCN05-1
CHCENCTN5M00004C
Efmody 5 mg
Modified-release
hard capsules
Hydrocortisone
For oral use
50 Modified-release
hard capsules
Read the package leaflet
before use.
Each capsule contains
5mg hydrocortisone.
Store in the original package.
Keep the bottle tightly closed in
order to protect from moisture.
Keep out of the sight and reach
of children.
EU/1/21/1549/001
Diurnal Europe B.V.,
Van Heuven Goedhartlaan 935 A,
1181LD Amstelveen, The Netherlands.
Efmody 5 mg
Modified-release
hard capsules
Hydrocortisone
For oral use
50 Modified-release
hard capsules
UKNI/UKGB
POM
PLGB 50616/0011
Text below to be printed in varnish free
area on-line during packaging.
Text is printed in order shown.
(X denotes any character, MM YYYY
denotes month/year in two digit/four
digit format).
PC 05060489090362
SN XXXXXXXXXXXXX
EXP MM YYYY
LOT XXXXXX


Read the package leaflet before use.
For oral use.
Each capsule contains
5 mg hydrocortisone.
Store in original package. Keep the
bottle tightly closed in order to protect
from moisture.
Keep out of the sight and reach of
children.
Diurnal Europe B.V.,
Van Heuven Goedhartlaan 935 A,
1181LD Amstelveen,
The Netherlands.
EU/1/21/1549/001
PLGB 50616/0011
Efmody 5 mg
Modified-release
hard capsules
Hydrocortisone
50 Modified-release hard capsules
LOT:
EXP:

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

Annex 1
Summary of fulfilment of the criteria for orphan drug designation

Products: Efmody 5, 10 & 20mg modified-release hard capsules
Active substance: Hydrocortisone
Orphan Designation Number: PLGB 50616/0011-0013

Background:
These applications were evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered to not be fulfilled.

Evaluation:
Orphan condition
The orphan condition is Congenital Adrenal Hyperplasia (CAH).

The condition of CAH is a distinct, heritable medical condition, caused by mutations in the genes encoding steroid hormone biosynthesis in the adrenal glands. Approximately 95% of CAH cases are caused by mutations in CYP21A2, the gene encoding adrenal steroid 21-hydroxylase and less commonly by mutations in 11-beta-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, 17-hydroxylase or the steroidogenic acute regulatory protein (STAR) gene.

In all cases, this leads to varying degrees of cortisol (glucocorticoid) and aldosterone (mineralocorticoid) deficiency. The low plasma cortisol leads to a feedback upregulation of adrenocorticotrophic hormone (ACTH) in an attempt to compensate for steroid deficiency. The elevated ACTH in turn results in the accumulation of steroid precursors progesterone, 17-hydroxypregnenolone, and in particular 17-hydroxyprogesterone (17 OHP) as a result of the downstream metabolic block in biosynthesis of cortisol due to enzyme deficiency. The accumulated 17-OHP is in turn diverted to synthesis of hormones with androgenic activity including dehydroepiandrosterone (DHEA), androstenedione (A4) and testosterone.

The clinical manifestations of CAH include those associated more generally with deficiency of corticosteroid hormones in a variety of adrenal insufficiency states. This may manifest as aesthenia, low blood pressure, electrolyte disturbance and a risk of adrenal crisis under conditions of physical or emotional stress. In addition, CAH is associated with androgen precursor accumulation leading to virilisation in females, premature development of sexual characteristics in males and infertility in both sexes.

While it is agreed that CAH exhibits features shared by other adrenal insufficiency states, it has distinct pathophysiological features that require careful management of corticosteroid replacement therapy in order to achieve adequate androgen precursor suppression while avoiding over-replacement and hypercortisolism with its attendant risks.

In November 2020, a panel of EU and UK endocrinologists was tasked by the Company to consider the conditions of adrenal insufficiency (AI) and CAH, using the DELHI panel method. The consensus (unanimous) opinion of the 18-member panel is that CAH is a distinct medical condition in its own right and is not sufficiently captured under the broader condition of adrenal insufficiency. AI and CAH are different in respect of aetiology, pathophysiology and symptomatology. The DELPHI report is supplied.

Orphan indication

The orphan indication is "*treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.*"

Life threatening/ debilitating condition
Without steroid replacement therapy, the condition is almost invariably fatal. Even with corticosteroid replacement therapy, patients are at risk of life-threatening adrenal crises. The consequences of androgen excess present additional challenges that may seriously impact quality of life in CAH.

In conclusion, it is agreed that the condition is both seriously debilitating and life-threatening.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the point prevalence is estimated to be approximately 0.8 in 10,000. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of treatment
The applicant accurately describes a range of licensed treatments that are used for corticosteroid replacement therapy and that may be used in CAH. These include a range of immediate-release formulations of hydrocortisone, including lower strength formulations suitable for the paediatric population; also, longer acting glucocorticoids – prednisone, prednisolone and dexamethasone which are generally only recommended in adults as second-line treatment after failure of immediate-release hydrocortisone.

The applicant also refers to a modified-release formulation of hydrocortisone – Plenadren – which is licensed for the treatment of adrenal insufficiency in adults. This is no longer considered relevant in the scope of licensed medicinal products to treat CAH. Plenadren is not considered an existing method of treatment in GB for CAH.

In conclusion, the applicant has considered existing methods that are available in GB.

Justification of significant benefit
Significant benefit over existing methods of treatment is evaluated for the proposed orphan indication specified in Section 4.1. The target population comprises adults and adolescents from the age of 12 years, with CAH. Although pivotal study data are confined to adults, extrapolation to adolescents can be agreed. The population-based pharmacokinetic modelling data to support this is not of itself adequate but extrapolation can be agreed on the basis of the recommendation for dose titration according to clinical need, as well as the recommendation for administration on the basis of body surface area in growing adolescents, combined with treatment oversight by a specialist practitioner.

The overall therapeutic aim of Efmody is to provide cortisol replacement over a 24-hour period that more closely mimics the normal diurnal pattern such that a nighttime rise in cortisol occurs, thereby avoiding feedback upregulation of ACTH during the night. The importance of avoiding high levels of ACTH is that this avoids accumulation of steroid precursors that are in turn diverted down a biosynthetic pathway leading to androgen excess owing to the metabolic block. Efmody is formulated as a modified release product that exhibits delayed, followed by sustained, release of hydrocortisone. It is administered in a twice daily regimen, titrated according to clinical need.

Standard of care glucocorticoid replacement therapy for adults and adolescents with CAH consists of immediate-release formulations of hydrocortisone that may need to be administered up to 4 times daily owing to the short elimination half-life of the active substance. This leads to fluctuations in plasma cortisol and declining levels of plasma cortisol during the night, with a corresponding rise in ACTH and circulating androgen precursors.

Higher potency glucocorticoids – prednisone, prednisolone and dexamethasone – that have a longer duration of action may also be used in adults with CAH as an alternative to immediate-release hydrocortisone. However, they are not recommended in the paediatric population due to the greater growth suppressive risks. In adults, prednisone is generally preferred to dexamethasone owing to the latter's greater propensity for Cushingoid side effects and potent growth suppression. Prednisone and dexamethasone also have an overall greater negative effect on bone density than hydrocortisone but this may be due to duration of action.

Both prednisone and dexamethasone have less mineralocorticoid effect than hydrocortisone and may therefore be less effective in salt-wasting forms of CAH.

Clinical practice guidelines continue to recommend immediate-release hydrocortisone as a first-line treatment for CAH patients of all ages.

The challenge with all standard of care glucocorticoid regimens in CAH is that in order to achieve sufficient suppression of ACTH, and thereby avoidance of androgen excess, through a 24-hour period, relative over-replacement is required, risking hypercortisolism. A balance therefore needs to be struck that may be non-optimal.

The applicant discusses a modified-release oral formulation of hydrocortisone – Plenadren – which is licensed in the UK for treatment of adrenal insufficiency in adults. We agree with the overall conclusion of the DELPHI panel of endocrinologists that CAH and adrenal insufficiency are distinct medical conditions. Plenadren is therefore not considered to be a licensed treatment for CAH and is, therefore, not relevant to the evaluation of significant benefit in the specific condition of CAH.

A pivotal study in 122 adults with CAH is supplied. This compared Efmody with standard of care glucocorticoid regimens. The study failed to meet its primary endpoint which was statistically significant superiority for change in 24-hour mean standard deviation score (SDS) for 17-OHP at 24 weeks. However, when this was broken down into different time windows over a 24 hour period, the window considered of most clinical relevance (early morning to 15:00) demonstrated a difference in 17-OHP SDS that was statistically significant, suggesting improved overnight suppression of ACTH and resultant avoidance of 17-OHP accumulation. This was evident at the 24-week time point as well as earlier time points. The area under the curve for 17-OHP was also lower for Efmody compared with standard of care. Responder analysis (decline of 17-OHP to target levels aimed for in clinical practice) also demonstrated a larger percentage of responders with Efmody compared with standard of care. The totality of the data therefore support that Efmody does exhibit a pharmacodynamic trend consistent with improved androgen suppression compared to standard of care glucocorticoid treatment. The CHMP conclusion of positive benefit-risk for Efmody in the treatment of CAH in patients aged 12 years and older is, therefore, supported.

Demonstration of positive benefit-risk is not of itself, however, sufficient to conclude significant benefit compared to existing methods of treatment.

It is agreed that the clinical study data overall provide clinical pharmacokinetic and pharmacodynamic evidence to support that Efmody is releasing hydrocortisone in the manner intended such that there is suppression of the nocturnal rise in ACTH which lowers the levels of the androgen precursors 17-OHP and A4 in the first part of the day.

What is missing, however, is evidence that this has translated into clinical outcomes indicative of clinically relevant advantage, such as clinically meaningful lessening of the effects of androgen excess on target tissues, or sparing from adverse effects of hypercortisolism arising from over-replacement.

The clinical endpoints body mass and bone mineral density were measured by DEXA scan in the pivotal study. The aim was to determine whether there was a relevant difference in total fat mass or bone mineral density (consistent with a reduction in hypercortisolism) for Efmody compared with standard of care glucocorticoids. No statistically significant difference was demonstrated.

Endpoints reflective of glycaemic control (fasting blood glucose and glycosylated haemoglobin) were also evaluated as markers of hypercortisolism but the differences seen are not considered reflective overall of improved glycaemic control.

There was also no difference in quality of life for patients receiving Efmody compared to standard of care glucocorticoids.

It may have been that the titration regimen was too aggressive so that sensitivity to detect a difference in these outcomes was impaired but whatever the reason, there were no statistically significant, clinically relevant differences in endpoints reflective of androgen suppression on target tissues, or sparing from hypercortisolism.

The applicant also performed a number of post-hoc comparisons with standard of care in the pivotal study as well as indirect comparisons with standard of care in the published literature. In the pivotal study there was no clear evidence of glucocorticoid sparing in patients receiving Efmody. In the pivotal 24-week primary analysis window there was no discernible change in hydrocortisone equivalent dose from baseline in patients on Efmody. Given the contention that sparing from hypercortisolism, while achieving androgen suppression is an advantage for this formulation, there is at present no robust evidence to support this. Indirect comparisons with published literature are not reliable for reasons including questions of comparability of populations; also, “optimal” or “reference” ranges of androgen levels used for glucocorticoid dose titration may vary in clinical practice.

The applicant acknowledges that fertility outcomes were not intended as a quantifiable outcome in the pivotal 005 and the follow-up 006 study. Two partner pregnancies were reported in male patients treated with Efmody in 005 and two further partner pregnancies in 006. Four out of 42 female patients treated with Efmody in study 005 developed a more regular menstrual cycle compared with one out of 36 patients treated with standard glucocorticoids.

The numbers reported are too small to draw any robust conclusions on benefit on reproductive function. The pivotal study was confined to adults and there are therefore no data on growth suppression.

Another issue is that the earliest Efmody can be given is from the age of 12 years which is the minimum age in the recommended posology. Therefore, even if Efmody may have

potential for improved androgen suppression, the delay in treatment initiation means that Efmody will be unable to prevent some of the more severe clinical manifestations of androgen excess that may be present from birth, such as ambiguous genitalia.

Overall it is agreed that Efmody on the basis of the available evidence exhibits a trend to improved androgen suppression compared to standard of care glucocorticoid replacement therapy in adults and it is reasonable to expect that this same trend will exist in the adolescent population. It is also acknowledged that adolescents may have greater potential to derive clinical benefit from a formulation with an optimised-release profile than if such treatment is delayed to adulthood. However, there are no clinical outcome data in adolescents to support that.

At present therefore there are insufficient data to confirm that the clinical pharmacokinetic and pharmacodynamic outcomes, supportive of hydrocortisone release as intended, have translated into clinically meaningful improvements in target tissues affected by prolonged androgen excess. There is also no evidence of clinically meaningful sparing from hypercortisolism and its adverse effects. Clinically relevant advantage or a major contribution to patient care have not been demonstrated.

In conclusion, significant benefit cannot be considered to have been demonstrated for Efmody compared to existing methods of treatment in the proposed target population

Conclusion:
Conclusion on non-acceptability of orphan designation
The applicant has not demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

Decision: Orphan designation refused

Date: 28 May 2021